

WHAT IS CLAIMED IS:

1 1. A leptin receptor (OB-R) polypeptide.

1 2. The leptin receptor of claim 1 characterized by

- 2 a) specific binding to leptin under physiological conditions;
- 3 b) expression at high levels in cells of the hypothalamus, and
- 4 expression at lower levels in adipose tissue, testes, heart, and brain; and
- 5 c) having sequence similarity to gp130 cytokine receptors.

1 3. The leptin receptor of claim 1 which is encoded by a nucleic acid which is

2 identifiable with a polymerase chain reaction (PCR) probe selected from group

3 consisting of a probe for clone 7 (forward primer SEQ ID NO:42 and reverse

4 primer SEQ ID NO:43), a probe for clone 11 (forward primer SEQ ID NO:44 and

5 reverse primer SEQ ID NO:45), and both clone 7 and clone 11.

1 4. The leptin receptor of claim 3, which is encoded by a nucleic acid which is

2 identifiable with a PCR probe selected from the group consisting of a probe for

3 clone 42 (forward primer SEQ ID NO:26 and reverse primer SEQ ID NO:46); a

4 probe for clone 46 (forward primer SEQ ID NO:47 and reverse primer SEQ ID

5 NO:48); a probe for clone 58 (forward primer SEQ ID NO:47 and reverse primer

6 SEQ ID NO:50); a probe for clone S14 (forward primer SEQ ID NO:51 and

7 reverse primer SEQ ID NO:52); and a probe for clone S3 (forward primer SEQ

8 ID NO:53 and reverse primer SEQ ID NO:54).

1 5. The leptin receptor of claim 1 which is selected from the group consisting

2 of OB-Ra, OB-Rb, OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof.

1 6. The leptin receptor of claim 1 which is selected from the group consisting

2 of:

- 3 a) N-terminal corresponding to OB-Ra through Lys<sup>889</sup> and C-terminal
- 4 corresponding to a C-terminal selected from the group consisting of OB-
- 5 Rb, OB-Rc, and OB-Rd after Lys<sup>889</sup>;
- 6 b) N-terminal corresponding to OB-Rb or OB-Rc through Lys<sup>889</sup>, and
- 7 C-terminal corresponding to OB-Ra or OB-Rd after Lys<sup>889</sup>;
- 8 c) N-terminal corresponding to OB-Rd through Lys<sup>889</sup>, and C-terminal
- 9 corresponding to OB-Ra, OB-Rb, or OB-Rc;
- 10 d) N-terminal corresponding to OB-R from Pro<sup>664</sup> to Lys<sup>889</sup>, and C-
- 11 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
- 12 e) N-terminal corresponding to OB-R from Met<sup>733</sup> to Lys<sup>889</sup>, and C-
- 13 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
- 14 f) N-terminal selected from the group consisting of OB-Ra, OB-Rb,
- 15 OB-Rd, and OB-R from Pro<sup>664</sup>, to His<sup>796</sup>, and OB-Re from His<sup>796</sup>;
- 16 g) N-terminal corresponding to OB-R from Met<sup>733</sup> to His<sup>796</sup>, and OB-Re
- 17 from His<sup>796</sup>, or allelic variants thereof.

1 7. The leptin receptor of claim 1 wherein

- 2 a) the N-terminal sequence is selected from the group consisting of
- 3 i) amino acid residues 1-889;
- 4 ii) amino acid residues 23-889;
- 5 iii) amino acid residues 28-889;
- 6 iv) amino acid residues 133-889;
- 7 v) amino acid residues 733-889;
- 8 vi) amino acid residues 1-796;
- 9 vii) amino acid residues 23-796;
- 10 viii) amino acid residues 28-796;
- 11 ix) amino acid residues 133-796; and
- 12 x) amino acid residues 733-796; and
- 13 b) the C-terminal sequence is selected from the group consisting of
- 14 i) SEQ ID NO:11;
- 15 ii) SEQ ID NO:12;

- 16                   iii)    SEQ ID NO:13;  
17                   iv)    SEQ ID NO:14; and  
18                   v)    SEQ ID NO:15;

19 wherein the numbering is based on the amino acid sequence of the full length  
20 transcribed murine leptin receptor, including the signal peptide, or allelic variants  
21 thereof.

1   8.     The leptin receptor of claim 1 which is a soluble receptor.

1   9.     The leptin receptor of claim 8 which is selected from the group consisting  
2 of

- 3           a)     OB-Re;  
4           b)     an N-terminal sequence which selected from the group consisting of  
5           OB-Ra, OB-Rb, OB-Rd, and OB-R from Pro<sup>664</sup>, through His<sup>799</sup>, and a C-  
6           terminal sequence which is OB-Re from His<sup>796</sup>;  
7           c)     an N-terminal sequence which is selected from the group consisting  
8 of  
9           i)     amino acid residues 1-796;  
10          ii)    amino acid residues 23-796;  
11          iii)   amino acid residues 28-796;  
12          iv)    amino acid residues 133-796; and  
13          v)     amino acid residues 733-796; and  
14          a C-terminal sequence which is SEQ ID NO:15;

15 wherein the numbering is based on the amino acid sequence of the full length  
16 transcribed murine leptin receptor, including the signal peptide, or allelic variants  
17 ~~thereof.~~

1   10.    The leptin receptor of claim 1 which ~~comprises a transmembrane domain,~~  
2 and is an integral membrane protein.

1 11. The leptin receptor of claim 10 which further comprises a JAK binding  
 2 motif selected from "Box 1," "Box 2," and "Box 1" and "Box 2", which motif is  
 3 downstream of the transmembrane domain.

1 12. The leptin receptor of claim 1 which is a human leptin receptor.

~~1 13. The leptin receptor of claim 1 which is a murine leptin receptor.~~

1 14. The leptin receptor of claim 12 comprising an amino acid substitution  
 2 selected from the group consisting of: Phe for Ser<sup>36</sup>; Asp for Tyr<sup>44</sup>; Ser for Leu<sup>49</sup>;  
 3 Pro for Ser<sup>54</sup>; Leu for Ser<sup>60</sup>; Ala for His<sup>63</sup>; Ala for Thr<sup>66</sup>; Ala for Pro<sup>70</sup>; Ile for  
 4 Thr<sup>77</sup>; Tyr for His<sup>78</sup>; Pro for Ser<sup>80</sup>; Gly for Arg<sup>92</sup>; Gly for Asp<sup>96</sup>; Thr for Ala<sup>103</sup> or  
 5 Ile<sup>106</sup>; Ser for Leu<sup>118</sup>; Gly for Asp<sup>124</sup>; Thr for Lys<sup>138</sup>; Pro for Ser<sup>146</sup>; Asp for Val<sup>164</sup>;  
 6 Leu for Gln<sup>177</sup>; Asp for Gly<sup>179</sup>; Gly for Glu<sup>192</sup>; deletion for Cys<sup>193</sup>; His for Leu<sup>197</sup>;  
 7 Ser for Ile<sup>221</sup>; Leu for Asn<sup>233</sup>; Leu for Ser<sup>273</sup>; deletion for Thr<sup>278</sup>; Ala for Asp<sup>285</sup>;  
 8 Glu for Lys<sup>286</sup>; Ser for Gly<sup>310</sup>; Arg for Met<sup>370</sup>; Ile for Ser<sup>379</sup>; Ser for Phe<sup>394</sup>; Ala for  
 9 Glu<sup>417</sup>; Gly for Glu<sup>459</sup>; Ser for Ile<sup>476</sup>; Thr for Ile<sup>482</sup>; Thr for Ile<sup>551</sup>; His for Tyr<sup>586</sup>;  
 10 Lys for Ile<sup>648</sup>; Ala for Ser<sup>686</sup>; His for Cys<sup>687</sup>; Thr for Ile<sup>759</sup>; Ile for Asn<sup>776</sup>; Asp for  
 11 Gly<sup>781</sup>; Gly for Glu<sup>782</sup>; Gly for Ser<sup>827</sup>; Ala for Asp<sup>832</sup>; Arg for Pro<sup>892</sup>; Thr for  
 12 Glu<sup>893</sup>; Asp for Thr<sup>894</sup>; or Leu for Glu<sup>896</sup>, wherein the numbering of the amino  
 13 acids corresponds to the numbering adopted for the human leptin receptor,  
 14 including the signal sequence.

1 15. An antigenic fragment of the leptin receptor of claim 1.

1 16. The antigenic fragment of claim 15 which is selected from the group  
 2 consisting of SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34.

1 17. A derivative of the leptin receptor of claim 8 or 9 attached to a chemical  
 2 moiety.

- 1 18. The derivative of claim 15 wherein the chemical moiety is a water-soluble  
2 polymer.
- 1 19. The derivative of claim 16 wherein the water soluble polymer is  
2 polyethylene glycol.
- 1 20. An isolated nucleic acid encoding a leptin receptor of claim 1.
- 1 21. An isolated nucleic acid encoding a leptin receptor of claim 5, 6, or 7.
- 1 22. An isolated nucleic acid encoding a leptin receptor of claim 8 or 9.
- 1 23. An isolated nucleic acid encoding a leptin receptor of claim 10 or 11.
- 1 24. An isolated DNA molecule encoding on expression a leptin receptor  
2 polypeptide selected from the group consisting of:  
3 a) a polypeptide coding sequence of a DNA molecule of SEQ ID  
4 NO:1, 3, 5, 7, or 9;  
5 b) a DNA molecule complementary to the DNA molecule defined in  
6 (a);  
7 c) a DNA molecule which hybridizes to the DNA molecule of (a) or  
8 (b), or a hybridizable fragment thereof;  
9 d) a DNA molecule which is identifiable with a polymerase chain  
10 reaction (PCR) probe selected from group consisting of a probe for clone 7  
11 (forward primer SEQ ID NO:42 and reverse primer SEQ ID NO:43), a  
12 probe for clone 11 (forward primer SEQ ID NO:44 and reverse primer  
13 SEQ ID NO:45), and both clone 7 and clone 11; and  
14 e) a DNA molecule that codes on expression for the polypeptide  
15 encoded by any of the foregoing DNA molecules.
- 1 25. The DNA molecule of claim 24 which is human.

1 26. The DNA molecule of claim 24 which is murine.

1 27. The DNA molecule of claim 24 which codes on expression for a  
2 polypeptide selected from the group consisting of:

3 a) a leptin receptor selected from the group consisting of OB-Ra, OB-  
4 Rb, OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof;

5 b) a leptin receptor selected from the group consisting of:

6 i) N-terminal corresponding to OB-Ra through Lys<sup>889</sup> and C-  
7 terminal corresponding to a C-terminal selected from the group  
8 consisting of OB-Rb, OB-Rc, and OB-Rd after Lys<sup>889</sup>;

9 ii) N-terminal corresponding to OB-Rb or OB-Rc through  
10 Lys<sup>889</sup>, and C-terminal corresponding to OB-Ra or OB-Rd after  
11 Lys<sup>889</sup>;

12 iii) N-terminal corresponding to OB-Rd through Lys<sup>889</sup>, and C-  
13 terminal corresponding to OB-Ra, OB-Rb, or OB-Rc;

14 iv) N-terminal corresponding to OB-R from Pro<sup>664</sup> to Lys<sup>889</sup>, and  
15 C-terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;

16 v) N-terminal corresponding to OB-R from Met<sup>733</sup> to Lys<sup>889</sup>, and  
17 C-terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;

18 vi) N-terminal selected from the group consisting of OB-Ra,  
19 OB-Rb, OB-Rd, and OB-R from Pro<sup>664</sup>, through His<sup>796</sup>, and OB-Re  
20 from His<sup>796</sup>, and

21 vii) N-terminal corresponding to OB-R from Met<sup>733</sup> to His<sup>796</sup>, and  
22 OB-Re from His<sup>796</sup>,

23 or allelic variants thereof;

24 c) a leptin receptor wherein

25 i) the N-terminal sequence is selected from the group consisting  
26 of

27 (1) amino acid residues 1-889;

28 (2) amino acid residues 23-889;

29 (3) amino acid residues 28-889;

- 30 (4) amino acid residues 133-889;  
31 (5) amino acid residues 733-889;  
32 (6) amino acid residues 1-796;  
33 (7) amino acid residues 23-796;  
34 (8) amino acid residues 28-796;  
35 (9) amino acid residues 133-796; and  
36 (10) amino acid residues 733-796; and  
37 ii) the C-terminal sequence is selected from the group consisting  
38 of  
39 (1) SEQ ID NO:11;  
40 (2) SEQ ID NO:12;  
41 (3) SEQ ID NO:13;  
42 (4) SEQ ID NO:14; and  
43 (5) SEQ ID NO:15;  
44 wherein the numbering is based on the amino acid sequence of the full  
45 length transcribed murine leptin receptor, including the signal peptide, or  
46 allelic variants thereof.

1 28. A nucleic acid molecule having a nucleotide sequence corresponding or  
2 complementary to the DNA sequence set forth in SEQ ID NO:1, 3, 5, 7 or 9.

1 29. An oligonucleotide hybridizable under stringent conditions to the nucleic  
2 acid molecule of claim 24.

1 30. An oligonucleotide hybridizable under stringent conditions to the nucleic  
2 acid molecule of claim 27.

1 31. An oligonucleotide hybridizable under stringent conditions to the nucleic  
2 acid molecule of claim 28.

1 32. The oligonucleotide of claim 29, 30, or 31 selected from the group  
2 consisting of SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23,  
3 SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID  
4 NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:35, SEQ  
5 ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40,  
6 SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID  
7 NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ  
8 ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, and SEQ ID  
9 NO:54.

1 33. The oligonucleotide of claim 32 which is labeled.

1 34. The nucleic acid of claim 20, 21, 22, or 23 which is DNA.

1 35. A vector comprising the DNA of claim 34.

1 36. A vector comprising the DNA of claim 24, 27, or 28.

1 37. An expression vector which comprises the DNA of claim 34, operatively  
2 associated with an expression control sequence.

1 38. An expression vector which comprises the DNA of claim 24, 27, or 28,  
2 operatively associated with an expression control sequence.

1 39. An unicellular host transformed or transfected with a DNA molecule of  
2 claim 34.

1 40. An unicellular host transformed or transfected with a DNA molecule of  
2 claim 24, 27, or 28.



1 41. An unicellular host transformed or transfected with an expression vector of  
2 claim 37.

1 42. An unicellular host transformed or transfected with an expression vector of  
2 claim 38.

1 43. The unicellular host of claim 41 selected from the group consisting of  
2 bacteria, yeast, mammalian cells, plant cells, and insect cells, in tissue culture.

1 44. The unicellular host of claim 42 selected from the group consisting of  
2 bacteria, yeast, mammalian cells, plant cells, and insect cells, in tissue culture.

1 45. The unicellular host of claim 43, wherein the unicellular host is selected  
2 from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*,  
3 *Saccharomyces*, *Pichia*, *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM,  
4 COS 1, COS 7, BSC1, BSC40, BMT10, and Sf9 cells.

1 46. The unicellular host of claim 44, wherein the unicellular host is selected  
2 from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*,  
3 *Saccharomyces*, *Pichia*, *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM,  
4 COS 1, COS 7, BSC1, BSC40, BMT10, and Sf9 cells.

1 47. A method for preparing a leptin receptor polypeptide comprising:  
2 a) culturing a cell according to any claim 43 under conditions that  
3 provide for expression of the leptin receptor polypeptide; and  
4 b) recovering the expressed polypeptide.

1 48. A method for preparing a leptin receptor polypeptide comprising:  
2 a) culturing a cell according to any claim 44 under conditions that  
3 provide for expression of the leptin receptor polypeptide; and  
4 b) recovering the expressed polypeptide.

- 1 49. The oligonucleotide of claim 29, 30, or 31 which is an antisense nucleic  
2 acid that hybridizes with an mRNA encoding leptin receptor.
- 1 50. A ribozyme which cleaves an mRNA encoding a leptin receptor.
- 1 51. A transgenic vector comprising a DNA molecule of claim 34.
- 1 52. A transgenic vector comprising a DNA molecule of claim 24, 27, or 28.
- 1 53. An antibody specific for a leptin receptor of claim 1.
- 1 54. An antibody according to claim 53 which is a monoclonal or polyclonal  
2 antibody.
- 1 55. An antibody according to claim 53 labeled with a detectable label.
- 1 56. An immortal cell line that produces a monoclonal antibody according to  
2 claim 54.
- 1 57. A method for preparing an antibody specific for a leptin receptor,  
2 comprising:  
3 a) immunizing a host animal with the leptin receptor of claim 1  
4 admixed with an adjuvant; and  
5 b) obtaining antibody from the immunized host animal.
- 1 58. A method for preparing an antibody specific for a leptin receptor,  
2 comprising:  
3 a) conjugating a peptide having a sequence selected from the group  
4 consisting of SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34 to a  
5 carrier protein;

- 6        b)        immunizing a host animal with the peptide-carrier protein conjugate
- 7        of step (a) admixed with an adjuvant; and
- 8        c)        obtaining antibody from the immunized host animal.

1    59.    A method for measuring the presence of a leptin receptor in a sample,  
2    comprising:  
3        a)        contacting a sample suspected of containing a leptin receptor with an  
4        antibody that specifically binds to the leptin receptor under conditions  
5        which allow for the formation of reaction complexes comprising the  
6        antibody and the leptin receptor; and  
7        b)        detecting the formation of reaction complexes comprising the  
8        antibody and leptin receptor in the sample,  
9    wherein detection of the formation of reaction complexes indicates the presence of  
10   leptin receptor in the sample.

1    60.    The method according to claim 59 wherein the antibody is bound to a solid  
2    phase support.

1    61.    An *in vitro* method for evaluating the level of leptin receptor in a biological  
2    sample comprising:  
3        a)        detecting the formation of reaction complexes in a biological sample  
4        according to the method of claim 59 or 60; and  
5        b)        evaluating the amount of reaction complexes formed, which amount  
6        of reaction complexes corresponds to the level of leptin receptor in the  
7        biological sample.

1    62.    An *in vitro* method for detecting or diagnosing the presence of a disease  
2    associated with elevated or decreased levels of leptin receptor in a subject  
3    comprising:

4           a)       evaluating the level of leptin receptor in a biological sample from a  
5           subject according to claim 61; and  
6           b)       comparing the level detected in step (a) to a level of leptin receptor  
7           present in normal subjects or in the subject at an earlier time,  
8   wherein an increase in the level of leptin receptor as compared to normal levels  
9   indicates a disease associated with elevated levels of leptin receptor, and decreased  
10   level of leptin receptor as compared to normal levels indicates a disease associated  
11   with decreased levels of leptin receptor.

1   63.    A pharmaceutical composition comprising a soluble leptin receptor  
2   according to any of claims 8 or 9, and a pharmaceutically acceptable carrier.

1   64.    A method for treating obesity in a subject comprising administering a  
2   therapeutically effective amount of the pharmaceutical composition of claim 63.

1   65.    The method according to claim 64, further comprising administering a  
2   treatment for diabetes, high blood pressure, and high cholesterol.

1   66.    A body appearance improving cosmetic composition for reducing the body  
2   weight of an individual comprising a soluble leptin receptor of claim 8 or 9, and  
3   an acceptable carrier.

Add a6